REMARKS

After entry of this amendment, claims 1-9, 12-13, 15-25, and 27-29 are pending. Claims 1 and 22 are amended and claims 10, 11, 14, 26, and 30-33 are canceled. The amendment to claims 1 and 22 are supported by original claims 2-4 and 23-25.

Examiner Interview

On August 26, 2009, Examiner Leslie A. Royds had a telephonic interview with attorneys for Applicants, Janet S. Hendrickson, John Roedel, Robert Patino, and Kristy Owen. The Examiner and the Applicants' representatives discussed the outstanding rejections. In particular, Applicants provided an amended claim for discussion that was substantially similar to amended claim 1. Examiner Royds indicated that the amendment would overcome the 35 U.S.C. 112 rejection, but when the discussion turned to the obviousness of the present claims in view of the cited art, no agreement was reached. Therefore, applicants have expanded the nonobviousness arguments presented in the interview in the response below.

35 U.S.C. § 112 Rejection

Reconsideration is respectfully requested of the rejection of claims 2-3, 5-9, and 23-24 under 35 U.S.C. § 112, second paragraph as failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 1 and 22 are amended and now require "prior to, simultaneous with, or subsequent to exposure to radiation for a time and at an intensity sufficient to result in alopecia." This claim element modifies radiation and describes its time and intensity and requires that it be sufficient to result in alopecia. As explained in the prior response for claims 30-33, because this radiation exposure requirement does not indicate that the radiation exposure occurs before or after administration of the methionine protectant agent, claim 30 neither requires nor suggests a temporal relationship between administration of the methionine protectant agent and the radiation exposure. Thus, claims 2-3, 5-9, and 23-24 satisfy the requirements of 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1-9, 11-13, 15-25, and 27-29 under 35 U.S.C. § 103 as being unpatentable over Pallenberg et al. (U.S. Patent No. 5,538,940) in view of Remington's Pharmaceutical Sciences (p. 702-703). Claim 1 is directed to a method for treating alopecia in a patient comprising exposing said patient in need thereof to radiation for a time and at an intensity sufficient to result in alopecia and orally or parenterally administering to said patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, and a pharmaceutically acceptable salt thereof.

Pallenberg discloses peptide-copper complexes that stimulate growth of hair in warm-blooded animals. The peptide-copper complexes have at least two amino acids (or amino acid derivatives), one of which is histidine, arginine or a derivative thereof. Thus, the peptide-copper complex is represented by formula A, where A is $[R_1\text{-}R_2]$:copper(II) wherein R_1 is an amino acid or an amino acid derivative, and R_2 is histidine, arginine or a derivative thereof.

The Office cites Remington's Pharmaceutical Sciences to support the assertion that parenteral administration provides rapid distribution of the agent throughout the bloodstream and that multiple dose administration can be used when the treatment needed cannot be provided in one dose.

Pallenberg does not disclose a methionine monomer or a salt thereof. Throughout the Pallenberg reference, the copper-peptide complexes are described and prepared as peptides and no amino acid monomers are disclosed or suggested for use in ameliorating alopecia or hair loss. Further, when methionine is discussed, it is in a laundry list of amino acids and described in a combination with arginine or histidine. Thus, the Pallenberg reference does not teach the use of D-methionine, L-methionine, or a mixture thereof as required by claims 1 and 22.

Further, since Pallenberg does not disclose the use of monomeric D- or L-methionine, it does not matter whether the copper-peptide complex in Pallenberg is a salt. However, for argument's sake, the specification describes the pharmaceutically or physiologically acceptable salts of methionine as follows.

> These compounds can be administered alone, or in combination with the other drug compounds discussed herein, in the form of the water-soluble acid, free base, or as physiologically acceptable salts, including acid addition salts formed with

> organic and inorganic acids, for example, hydrochlorides, hydrobromides, sulfates, phosphates, citrates, fumarates, and maleates, and cations such as sodium, potassium, etc.[1]

Throughout the Pallenberg reference, the agents are described as peptide-copper complexes and cannot be considered salts when the term "salt" is construed with its ordinary meaning. A "complex" is a coordination compound where typically the s and p electrons interact with the d orbitals of the metal to form a chemical bond. In contrast, a salt is formed when a positive ion and a negative ion are associated with an ionic bond. The description in the instant specification is consistent with the construction of the "salt" term as not including a coordination compound. Further, Pallenberg repeatedly and consistently refers to its compounds as complexes and not salts as the Office asserts.[2] Thus, the peptide-copper complexes of Pallenberg are not within the scope of claims 1 and 22.

Further, contrary to the Office's assertion, Pallenberg does not render the instant claims obvious. The Examination Guidelines for Determining Obviousness in view of *KSR International Co. v. Teleflex Inc.* states that

> [t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious...there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.[3]

The Office has not provided articulated reasoning with some rational underpinning as to why the artisan would have found the claimed invention to have been obvious. To the contrary, the Office's assertion picks the portion of the Pallenberg reference that describes the use of methionine as one of 20 naturally occurring amino acids that can be used in a copper-peptide complex, but fails to mention that none of the representative complexes described in Table 1 includes methionine or a peptide including methionine as a ligand. Thus, the Pallenberg reference as a whole would have led a person of skill in the art away from administering methionine, D-methionine, L-methionine, or a salt thereof for treating radiation-induced alopecia. Further, Pallenberg does not provide any reason that a skilled person would have

[1] See specification at page 30, lines 11-18.
[2] Even though the examples discuss the synthesis of various dipeptides and tripeptides and disclose them as salts, the active ingredient for treating hair loss is a copper-peptide complexes and not the dipeptides or tripeptides.
[3] See Fed. Reg., 72(195), October 10, 2007, page 57526, 57528-57529.

believed that monomeric methionine without being included in a peptide or complexed to copper would affect radiation-induced alopecia. Thus, contrary to the Office's assertion, there would not have been a reasonable expectation that use of monomeric methionine was equivalent to the Pallenberg complexes as a protectant for alopecia arising from radiation exposure as required by claims 1 and 22.

Further, the Remington's Pharmaceutical Sciences does not remedy the deficiencies of the Pallenberg reference. Remington's Pharmaceutical Sciences is cited for general information regarding the route of administration and dosing regimen for therapeutic agents and does not provide any information regarding the activity of methionine, D-methionine, L-methionine, or a salt thereof for treating radiation-induced alopecia.

Therefore, claims 1-9, 11-13, 15-25, and 27-29 are patentable over Pallenberg et al. (U.S. Patent No. 5,538,940) in view of Remington's Pharmaceutical Sciences (p. 702-703) under 35 U.S.C. § 103.

Moreover, claims 1 and 22, and the claims that depend therefrom are patentable under 35 U.S.C. 103(a) over Pallenberg et al. (U.S. Patent No. 5,538,940) in view of Remington's Pharmaceutical Sciences (p. 702-703) when evaluating non-obviousness per PTO Guidelines Under *KSR* as published in M.P.E.P. § 2143.

The Guidelines enumerate and explain seven separate grounds for finding obviousness under *KSR*. They are:

(A) combining prior art elements according to known methods to yield predictable results;

(B) simple substitution of one known element for another to yield predictable results;

(C) use of known technique to improve similar devices in the same way;

(D) applying a known technique to a known device ready for improvement to yield predictable results;

(E) "obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) known work in one field of endeavor may prompt variations of it for use in the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or

(G) some teaching, suggestion, or motivation in the art that would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Each ground requires several factual inquiries. In addition to other findings which vary among the seven separate grounds, each of them requires a finding of predictable results. Enumerated grounds (A) through (F) of the Guidelines all expressly require a showing of predictable results, while ground (G) is the conventional motivation test as applied by the Federal Circuit substantially since the inception of that court. The motivation test as laid out in Ground (G) also requires predictable results, expressed in terms of "a reasonable expectation of success."

For example, with respect to Ground (A), the evidence shows that each element is not merely performing the same function as it did separately. Instead the elements of administering methionine, D-methionine, L-methionine, or a salt thereof to treat alopecia in a patient exposed to radiation and being in need of treatment is a new combination of the elements and monomeric methionine (without being in a copper complex) is a subtraction of elements and was not known from the cited references to treat alopecia in a patient in need thereof and exposed to radiation. While methionine has been administered to patients for other purposes, the methionine was not administered to treat alopecia in patients exposed to radiation and in need of treatment and from a contemplation of the cited art, it would not have been predictable that administration of methionine to treat alopecia in a patient exposed to radiation and in need of treatment would have been beneficial.

With respect to Ground (B), the inventors did not merely substitute one element for another, but starting with Pallenberg, the instant methods would have been a subtraction of the copper and peptide elements of the copper-peptide complex to arrive at the use of monomeric methionine to treat alopecia. For proper rejection on this ground, there must be a known and finite number of alternative elements to choose from and/or there must be known similarity in structure and function between the element required by the claim and that taught by the art. Neither is the case here. There are vast differences between monomeric methionine and copper-peptide complexes with respect to both structure and known function and none of the cited references establish any equivalence of function between the monomeric methionine and the

copper-peptide complexes. That the Pallenberg copper-peptide complexes can contain monomeric methionine as a component of a peptide ligand does not create a structural similarity that one skilled in the art would consider significant, and it would certainly fail to provide any basis for expectation of similar properties. Nor is there any art of record that suggests copper-peptide complexes and methionine have any similarity in function for any relevant purpose. The patient population to be treated by the method was those patients exposed to radiation and in need of treatment for alopecia. It would not have been predictable from a contemplation of the prior art that administering methionine to a patient in need of treatment for alopecia would have provided a beneficial effect.

No basis other than hindsight could support the alternative perception that administration of methionine to treat a patient suffering from radiation-induced alopecia should somehow be "substituted" in the method of Pallenberg where a copper-peptide complex is administered. One skilled in the art and concerned with treatment of radiation-induced alopecia would simply not have modified the copper-peptide complexes of Pallenberg to arrive at the instant claims.

The same applies to Ground (C). It makes no sense to start with a "base" method such as that disclosed by Pallenberg wherein a copper-peptide complex is used to treat alopecia in patients undergoing radiation treatment. Further, the advantageous effects of the administration of methionine for treating alopecia in a patient exposed to radiation and in need of treatment would not have been predictable to a person of skill in the art from the cited references or knowledge in the art.

The analysis of Ground (D) is similar to that of Ground (C). In neither case could a base method have been selected to which a known technique could have been applied to achieve any predictable result. If Pallenberg were deemed a "known [process] ready for improvement," there is no basis in either Pallenberg or Remington's Pharmaceutical Sciences for substituting methionine for copper-peptide complexes since the structures of methionine and the copper-peptide complexes are grossly different, one skilled in the art would have expected their physiological effects to be entirely different, and one skilled in the art would not have known that methionine and the copper-peptide complexes shared any property relevant to the treatment of alopecia. Further, as in the case of Ground (C), the advantageous effects of the administration of methionine for treating alopecia in a patient exposed to radiation and in need of treatment

would not have been predictable to a person of skill in the art from the cited references or knowledge in the art.

There is no evidence of any measure that was "obvious to try" in support of Ground (E). Administration of methionine to a patient exposed to radiation and in need of treatment for alopecia was not known and was not "obvious to try." Further, there were not a finite number of solutions that could be varied with predictable results because the results were unpredictable.

As to Ground (F), there is no evidence that either the field of endeavor or a different field included an analogous method, at least not any method that is more relevant than that of Pallenberg. The differences between the method of claims 1 and 22 and Pallenberg were not encompassed by any known variations or in any principle known to the art. Assuming *arguendo* that it was known that methionine treated side effects of various treatments, there was no known variation or principle which suggested that a patient exposed to radiation and in need of treatment for alopecia would have benefitted from the administration of methionine.

As noted, Ground (G) is the conventional motivation test as long applied by the Federal Circuit. There was no motivation in the art to administer methionine to a patient exposed to radiation and in need of treatment for alopecia. Although the side effect of alopecia in patients receiving radiation treatments for various conditions was known, the art did not suggest a way to alleviate alopecia that was in any way comparable to the instantly claimed method. Thus, there was no teaching, motivation or suggestion in the art to try methionine or any amino acid as a treatment for alopecia without complexing it to a copper ion. Further, there was not a reasonable expectation that administration of methionine to a patient exposed to radiation and in need of treatment for alopecia would have had a beneficial effect.

Moreover, there is no reason provided why a skilled person would have substituted methionine for the copper-peptide complex of Pallenberg to treat alopecia resulting from radiation exposure. A skilled person would have attributed the anti-alopecia effect of the copper-peptide complex to the specific structural aspects of the copper complex and not solely or primarily to the presence of a methionine ligand on the copper ion. A skilled person would not have expected D-methionine, L-methionine, or D,L-methionine, a 150 Dalton small molecule amino acid, to provide the same physiological effect as the copper-peptide complex, regardless of whether a methionine ligand happens to be present in the complex. Furthermore, the

representative copper-peptide complexes of Pallenberg do not include methionine. Even if in the unlikely event that methionine is somehow instrumental in imparting significant properties to the copper-peptide complex, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. Thus, a person of ordinary skill would not have expected methionine by itself to be an effective agent against alopecia based on the Pallenberg disclosure alone or as combined with the Remington's Pharmaceutical Sciences.

In order to further distinguish the amino acid protective agents encompassed by the instant claims from the copper-peptide complexes, the instant amendment limits the protective agent to "D-methionine, L-methionine, or D,L-methionine," each of which unambiguously denotes a monomeric amino acid and therefore does not read on copper-peptide complexes.

Applicant respectfully reserves the right to pursue a continuation application which claims the method in the terms stated in the claims prior to the instant amendment.

CONCLUSION

Applicant submits that the present application is in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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